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SYNTHESIS OF THE α-MANNOSIDASE INHIBITORS SWAINSONINE [(1S, 2R, 8R, 8aR)-1,2,8-TRIHYDROXYOCTAHYDROINDOLIZINE] AND 1,4-DIDEOXY-1,4-IMINO-D-MANNITOL FROM MANNOSE

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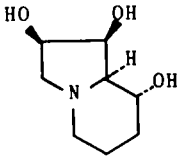
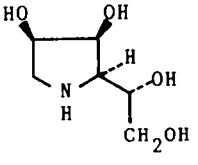
Benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside is a key intermediate in the syntheses of the α-mannosidase inhibitors, swainsonine [(1S, 2R, 8R, 8aR)-1,2,8-trihydroxyoctahydroindolizine] and 1,4-dideoxy-1,4-imino-D-mannitol, and of the α-galactosidase inhibitor 1,4-dideoxy-1,4-imino-D-lyxitol, from mannose.

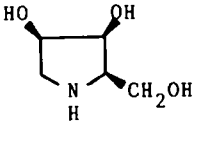
Swainsonine (1), initially isolated from plants,[1,2] has more recently been found in fungal species.[3,4] The numerous effects of swainsonine on viruses and on animal and plant cells arise from direct or indirect results of the inhibition of a mannosidase of glycoprotein processing;[5] it has recently been reported that swainsonine can stimulate the immune response.[6] 1,4-Dideoxy-1,4-imino-D-mannitol (2) is an azafuranose analogue of mannose and is structurally related to swainsonine but lacks the ethano unit connecting the nitrogen to C-6; (2) is also a powerful and specific inhibitor of several mannosidases,[7] including glycoprotein mannosidases.[8,9] It is noteworthy that the azafuranose analogues (1) and (2) have a different mannosidase inhibition profile than does the azapyranose analogue, deoxymannojirimycin.[10] 1,4-Dideoxy-1,4-imino-D-lyxitol (3) is a powerful inhibitor of α-galactosidase;[11] other 1,4-dideoxy-1,4-iminopentitols have also been shown to be glycosidase inhibitors.[12] This paper reports the synthesis of (1) (2) and (3) in which the pyrrolidine ring is constructed from D-mannose by intramolecular reductive aminations of suitably protected derivatives of 4-amino-4-deoxy-D-mannose (4); an efficient synthesis of the key intermediate benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (11) is described. Several other syntheses of swainsonine (1) have been reported,[13] but no other syntheses of (2) and (3) have appeared; some of the work in this paper has been published in a preliminary form.[7,11,14]



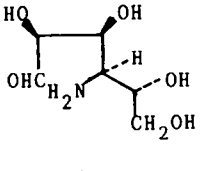
(1)



(2)



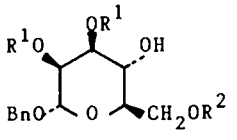
(3)



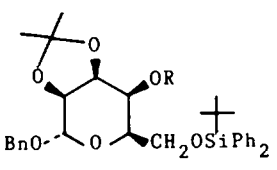
(4)

The preparation of benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (11) from D-mannose required access to the C-4 OH group while all the other functionalities of the sugar were protected. First, D-mannose was converted into benzyl α-D-mannopyranoside (5) by modification of a literature procedure.[15] Mannose was treated with benzyl alcohol containing hydrogen chloride at 50°C and subsequent addition of ether - petroleum ether caused the glycoside (5) to crystallise; yields obtained in this manner (83%) were higher than those

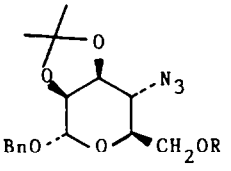
previously reported.[16] Acetonation of (5) gave complex reaction mixtures and so the primary hydroxyl group was selectively protected as the tert-butyldiphenylsilyl ether (6) [97% yield]. The 2,3-cis diol unit in (6) was then blocked using 2,2-dimethoxypropane in acetone in the presence of 10-camphor sulphonic acid to give (7) in which only the C-4 OH group of mannose is unprotected [quantitative yield; 81% yield from D-mannose].



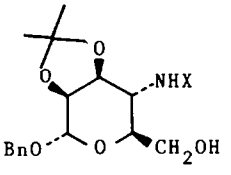
(5) $R^1 = R^2 = H$
(6) $R^1 = H$; $R^2 = SiPh_2Bu^t$
(7) $R^1 = Me_2C$; $R^2 = SiPh_2Bu^t$



(8) R = H
(9) $R = SO_2CF_3$



(10) $R = SiPh_2Bu^t$
(11) R = H



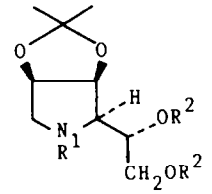
(12) X = H
(13) $X = COOCH_2Ph$

The preparation of the manno-azide (11) requires introduction of the nitrogen function at C-4 of (7) with overall retention of configuration; this was achieved by a sequence of reactions which result in double inversion. Treatment of the mannoside (7) with pyridinium chlorochromate in the presence of molecular sieve[17] gave an intermediate ketone which on reduction with sodium borohydride in ethanol gave the taloside (8) [88% yield from (7)] in which reduction of the ketone occurs from the least hindered equatorial face of the carbonyl group; other examples of highly efficient epimerisations of mannopyranosides to talopyranosides have been reported.[18] The talo alcohol (8) was esterified with trifluoromethanesulphonic anhydride at -10°C over three hours to give the triflate (9). Some indication of the steric environment of the C-4 OH group is obtained by the reaction time for the formation of the triflate; the trifluoromethanesulphonation of primary hydroxyl groups is normally completed in 5-10 minutes at -30°C and that of secondary hydroxyl groups is completed in 30-60 minutes at -30°C, with longer times being recorded for axial substitutents. The triflate (9) was treated with a suspension of sodium azide in dimethyl formamide at room temperature to give a mixture of the manno-azide (10) [68% yield], together with the elimination product, benzyl 4-deoxy-6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-erythro-hex-4-enopyranoside [24% yield]. Attempted displacement of the mesylate group from the methanesulphonate ester of (8) by azide in dimethylformamide gave only 40% of the azide (9) after 3 days at 150°C; it is therefore much more efficient to use the triflate rather than the mesylate in this sequence of reactions. The silyl protecting group was removed from (10) by treatment with tetrabutylammonium fluoride to give the easily crystallised benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (11) in 97% yield [46% overall yield from mannose].

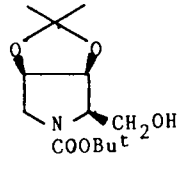
Catalytic hydrogenation of the azide (11) with palladium black in methanol gave a quantitative yield of the corresponding amine (12); protection of the amine (12) with benzylchloroformate gave the easily crystallised carbamate (13) in 80% yield from (11). Further hydrogenation of the amine (12) in the presence of palladium black in glacial acetic acid resulted in slow hydrogenolysis of the anomeric benzyl protecting group, followed by intramolecular reductive amination to give the isopropylidene pyrrolidine (14) in 90% yield. It is necessary to change solvent for the hydrogenation after the azide has been reduced to the amine; prolonged hydrogenation in methanol causes the N-methylation of amines; attempts to hydrogenate the azide (11) to the pyrrolidine (14) in acetic acid directly gave complex reaction mixtures. The isopropylidene protected pyrrolidine (14), which

could be converted to the crystalline triacetate (15) by treatment with acetic anhydride in pyridine, on treatment with trifluoroacetic acid in deuterium oxide gave the unprotected 1,4-dideoxy-1,4-imino-D-mannitol (2) in 73% yield [65% yield from (11); 30% from mannose]. The final removal of acid labile protecting groups was performed in deuterium oxide so that the progress of the deprotection could be readily followed by 60 MHz NMR spectroscopy. The mannosidase inhibitor (2), which is a hygroscopic solid, is more easily handled as the crystalline hydrochloride.

The presence of a diol side chain in (14) was shown by conversion of (14) into 1,4-dideoxy-1,4-imino-D-lyxitol. Thus reaction of (14) with di-tert-butyldicarbonate gave the diol (16) which on oxidation with sodium periodate followed by reduction of the resulting aldehyde with sodium borohydride gave the protected lyxitol (17) [35% yield from (14)]. Both the tert-butyloxycarbonyl and isopropylidene protecting groups were removed from (17) by treatment with trifluoroacetic acid in deuterium oxide to give the α-galactosidase inhibitor, 1,4-dideoxy-1,4-imino-D-lyxitol (3) [68% yield], more easily handled as the corresponding crystalline hydrochloride. A more convenient and efficient synthesis of (3) from D-glucose is described in the following paper.[19]



(14) $R^1 = R^2 = H$
(15) $R^1 = R^2 = COCH_3$
(16) $R^1 = COOBu^t$; $R^2 = H$



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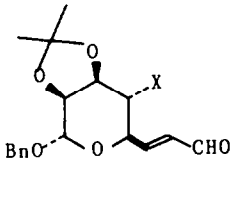
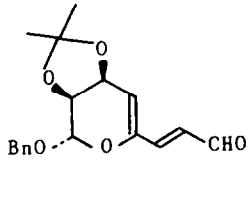
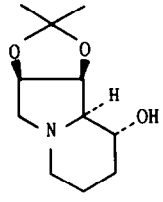


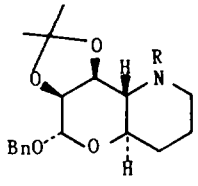
(18) X = N_3
(19) X = NHZ



(20)



(21)



(22) R = H
(23) R = Me

The synthesis of swainsonine (1) requires a two carbon chain extension from the primary alcohol in the azidoalcohol (11). Treatment of (11) with pyridinium chlorochromate in the presence of molecular sieve gave, after 45 minutes, the corresponding aldehyde. It was found to be convenient experimentally to add excess formylmethylene triphenylphosphorane at this point directly to the reaction mixture without any preliminary work-up. This allowed isolation of the E-azidoenal (18) consistently in the range of 60-65% on a 300 mg scale, although lower yields were obtained when the sequence was attempted on a larger scale. Of the other products produced by the reaction, the dieneal (20) was easily isolated. The problems associated with this two carbon chain extension probably arise from elimination of hydrazoic acid from the intermediate aldehyde, so that the two carbon extension from the benzyloxycarbonyl protected amine (13) was also investigated. Thus oxidation of (13) by pyridinium chlorochromate in the presence of molecular sieve

to give the corresponding aldehyde in 75% yield which was relatively more stable and could be characterised; when this aldehyde was treated with excess formylmethylene triphenylphosphorane, the required aldehyde (19) was isolated in 59% yield; thus there is no advantage in using the carbamate (13) rather than the azide (11) for the carbon extension sequence.

Treatment of the azidoaldehyde (18) with pre-reduced 10% palladium on carbon in methanol gave the isopropylidene protected bicyclic amine (22) cleanly after six hours at room temperature; this conversion requires the uptake of three equivalents of hydrogen in which the azide is reduced to an amine, the carbon-carbon double bond is reduced to a single bond and subsequently an intramolecular reductive amination occurs. However, under these conditions, the cleavage of the anomeric benzyl protecting group is very slow and competitive N-methylation to give the tertiary amine (23) occurs. Accordingly, after the hydrogenation of the azidoaldehyde to the piperidine (22) was complete, the catalyst and solvent were removed, the residue was dissolved in acetic acid and subjected to further hydrogenation in the presence of pre-reduced palladium black; this procedure resulted in cleavage of the benzyl acetal followed by a second intramolecular reductive amination to give the acetonide of swainsonine (21).[2] The conversion of the azidoenal (18) to the protected swainsonine (21) requires the uptake of five equivalents of hydrogen and proceeds in an overall yield of 87%. When the carbamate (19) was hydrogenated in the presence of palladium black sequentially in methanol and then acetic acid, a similar course of reactions took place to produce (21) in 60% yield. Finally, the isopropylidene protecting group was removed from (21) by treatment with aqueous trifluoroacetic acid at room temperature for two days to give swainsonine (1), identical to an authentic sample,[20] in 75% yield. This final hydrolysis is slow since initial protonation of the nitrogen function reduces the rate of hydrolysis of the protecting group.

In summary this paper reports the synthesis of the α-mannosidase inhibitors, swainsonine and 1,4-dideoxy-1,4-imino-D-mannitol, and of the α-galactosidase inhibitor 1,4-dideoxy-1,4-imino-D-lyxitol, from mannose by a procedure in which the pyrrolidine ring is formed by joining C-1 and C-4 of mannose by nitrogen; the accompanying paper describes the synthesis of a number of polyhydroxylated pyrrolidines by joining C-3 and C-6 of glucose by nitrogen.[19,21]

Experimental

M.p.s were recorded on a Kofler block. Infra red spectra were recorded on a Perkin-Elmer 297 spectrophotometer in chloroform except where otherwise stated. ^{1}H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer (500 MHz on a Bruker AM 500 spectrometer); ^{13}C NMR spectra were recorded on a Bruker AM 250 (62.9 MHz) or a Bruker AM 500 (125.0 MHz) spectrometer. All ^{13}C NMR spectra were obtained using deuteriochloroform as solvent unless otherwise stated; for ^{13}C NMR spectra in D_2O, 1,4-dioxane (δ 67.6) was used as the internal standard. Mass spectra were recorded on VG Micromass ZAB 1F or MM 30F spectrometers; in order to obtain satisfactory mass spectra for these highly polar compounds, it was necessary to use DCI or FAB techniques. Microanalyses were performed by the microanalytical services of the Dyson Perrins Laboratory or of the Chemistry Department of Manchester University. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a spray of 5% v/v sulphuric acid in ethanol or a solution of 5% dodecamolybdophosphoric acid in ethanol. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh. Tetrahydrofuran was distilled from a solution dried with sodium in the presence of benzophenone under dry nitrogen. D-Mannose was obtained from Sigma Chemical Company, and formylmethylene

triphenylphosphorane was obtained from Lancaster Synthesis; both compounds were used without purification.

Benzyl α-D-Mannopyranoside (5). A suspension of D-mannose (50.7 g, 281 mmol) in benzyl alcohol (440 ml) containing acetyl chloride (20 ml, 281 mmol) was heated at 50°C for 1.5 h and then cooled to room temperature and stored for 24 h. The solution was diluted with ether (190 ml) and hexane (300 ml) and refrigerated for a further 24 h to enable crystallisation of the product. The precipitate was collected by filtration and re-crystallised from hot ethyl acetate to give benzyl α-D-mannopyranoside (5), (59.3 g, 83%), m.p. 130-132°C (lit.[15] 131-132°C).

Benzyl 6-O-tert-Butyldiphenylsilyl-α-D-mannopyranoside (6). tert-Butylchlorodiphenylsilane (20 ml, 78.0 mmol) was added dropwise to a solution of benzyl α-D-mannopyranoside (5) (6.7 g, 62.0 mmol) and imidazole (10.6 g, 136.0 mmol) in dry dimethylformamide (200 ml) and stirred for 6 h at room temperature. The solvent was evaporated and the residue dissolved in chloroform, washed with 5% hydrochloric acid followed by water and the organic layer was dried (magnesium sulphate). The solution was filtered and the solvent removed to give a syrup which was filtered through a silica gel plug (ethyl acetate : hexane) to give benzyl 6-O-tert-butyldiphenylsilyl-α-D-mannopyranoside (6), (28.1 g, 55 mmol, 89%), as a colourless syrup, $[\alpha]_D^{20}$ +30.1° (c, 3.0 in $CHCl_3$). ν_{max} ($CHCl_3$) 3600-3400 cm^{-1}. ^1H NMR δ 1.08 (9H, s, tBu); 2.51 (1H, d, OH); 2.90 (1H, d, OH); 3.18 (1H, d, OH); 3.69-3.98 (6H, m, 2-H, 3-H, 4-H, 5-H, 6-H); 4.55 (2H, ABq, $PhCH_2$); 4.89 (1H, s, 1-H); 7.3-7.9 (15H, m, ArH). m/z (DCI, NH_3): 526 ($M + NH_4^+$), 91 (100%).

Benzyl 6-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-α-D-mannopyranoside (7). A solution of benzyl 6-O-tert-butyldiphenylsilyl-α-D-mannopyranoside (6) (28.1 g, 55.0 mmol) in acetone (220 ml) and 2,2'-dimethoxypropane (30 ml) was stirred with camphorsulphonic acid (100 mg) at room temperature for 16 h. The mixture was neutralised with concentrated aqueous ammonium hydroxide and the solvent removed. The residue was dissolved in chloroform, washed with water and brine, and the organic layer subsequently dried. The solution was filtered and the solvent evaporated to give a syrup which was filtered through a silica plug (ether : hexane) to give benzyl 6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-mannopyranoside (7), (29.2 g, 97%), as a colourless syrup, $[\alpha]_D^{20}$ +14.2° (c, 1.6 in $CHCl_3$). ν_{max} ($CHCl_3$) 3500 cm^{-1}. ^1H NMR δ 1.1 (9H, s, tBu); 1.35 (3H, s, CH_3); 1.51 (3H, s, CH_3); 2.71 (1H, d, OH); 3.76 (2H, m, 6-H); 3.90 (2H, m, 4-H, 5-H); 4.19 (2H, m, 2-H, 3-H); 4.59 (2H, ABq, $PhCH_2$); 4.09 (1H, s, 1-H); 7.27-7.74 (15H, m, ArH). m/z (DCI, NH_3): 566 ($M + NH_4^+$), 548.

Benzyl 6-O-tert-Butyldiphenylsilyl-2,3-O-isopropylidene-α-D-talopyranoside (8). A mixture of benzyl 6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-mannopyranoside (7) (29.2 g, 53.0 mmol), pyridinium chlorochromate (34.1 g, 160 mmol) and powdered molecular sieve (3A, 34 g) in dichloromethane (200 ml) was stirred at room temperature for 2 h. The mixture was diluted with ether-hexane (1:1) and filtered through a silica gel plug. The colourless solution obtained was evaporated to give a syrup containing the crude ketone [ν_{max} 1736 cm^{-1}], which was dissolved in ethanol (100 ml). To the resulting solution, sodium borohydride (4.1g, 110.0 mmol) was added at 0°C. The reaction mixture was stirred for 1 h, quenched with solid ammonium chloride and the solvent removed. The residue was dissolved in chloroform, washed with water, dried and evaporated. Evaporation of the solvent gave benzyl 6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-talopyranoside (8), (23.3 g, 81%), as a colourless syrup, $[\alpha]_D^{20}$ +21.5° (c, 1.1 in $CHCl_3$). ν_{max}

($CHCl_3$) 3570 cm^{-1}. ^1H NMR δ 1.07 (9H, s, tBu); 1.39 (3H, s, CH_3); 1.57 (3H, s, CH_3); 2.25 (1H, d, OH); 3.81-3.93 (4H, m, 4-H, 5-H, 6-H); 4.13 (1H, d, 2-H); 4.26 (1H, t, 3-H); 4.66 (2H, ABq, $PhCH_2$); 5.18 (1H, s, 1-H); 7.3-7.9 (15H, m, ArH). m/z (DCI, NH_3): 566 ($M + NH_4^+$), 91 (100%) (Found : C, 69.76; H, 7.36. $C_{32}H_{40}O_6Si$ requires C, 70.04; H, 7.35%).

Benzyl 4-Azido-6-O-tert-butyldiphenylsilyl-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (10). Trifluoromethanesulphonic anhydride (1.9 ml, 11.3 mmol) was added dropwise to a solution of benzyl 6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-talopyranoside (8) (4.3 g, 7.9 mmol) in dichloromethane (50 ml) containing pyridine (2.5 ml) at -50°C. The solution was stored at -20°C for 8 h. The reaction was quenched by the addition of methanol (5 ml), diluted with dichloromethane and washed successively with saturated sodium bicarbonate solution, water and brine and then the organic layer was dried. The solvent was removed to give a red syrup containing the crude triflate (9) which was not purified. The crude triflate (9) was dissolved in dimethylformamide (50 ml) and sodium azide (1.8 g, 28.0 mmol) was added at room temperature. The suspension was then stirred at room temperature for 16 h. The solvent was evaporated and the residue dissolved in chloroform, washed with water and brine and then dried. Evaporation of the solvent and purification of the residue by flash chromatography (ether : hexane, 1:10) gave benzyl 4-azido-6-O-tert-butyldiphenylsilyl-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (10), (3.1 g, 68%), as a colourless syrup, $[\alpha]_D^{20}$ +15.6° (c, 1.1 in $CHCl_3$). υ_{max} ($CHCl_3$) 2120 cm^{-1}. ^1H NMR δ 1.09 (9H, s, tBu); 1.38 (3H, s, CH_3); 1.57 (3H, s, CH_3); 3.55 (1H, dt, 5-H); 3.75 (1H, dd, 4-H); 3.86 (2H, m, 6-H); 4.15 (1H, d, 2-H); 4.24 (1H, dd, 3-H); 4.59 (2H, ABq, $PhCH_2$); 5.15 (1H, s, 1-H); 7.3-7.8 (15H, m, ArH). m/z (DCI, NH_3) 591 ($M + NH_4^+$,1%), 488 (6%), 241 (46%),and 91 (100%). Also a minor product was obtained from the reaction identified as benzyl 6-O-tert-butyldiphenylsilyl-2,3-O-isopropylidene-α-D-erythro-hex-4-enopyranoside, (1.0 g, 24%), a colourless oil, ^1H NMR δ 1.08 (9H, s, tBu); 1.32 (3H, s, CH_3); 1.52 (3H, s, CH_3); 3.76 (2H, m, 6-H); 4.35 (1H, m, 2-H); 4.52-4.97 (4H, m, 1-H, 3-H and $PhCH_2$); 5.35 (1H, m, 4-H); 7.3-7.8 (15H, m, ArH). m/z (DCI, NH_3): 531 ($M + H^+$), 91 (100%).

Benzyl 4-Azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (11). A solution of benzyl 4-azido-6-O-tert-butyldiphenylsilyl-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (10) (2.99 g, 5.1 mmol) in tetrahydrofuran (35 ml) containing tetrabutylammonium fluoride (1M solution in tetrahydrofuran, 10.2 ml, 10.2 mmol) was stirred at room temperature for 4 h. The solvent was removed and the residue dissolved in chloroform and washed with water, then brine and the organic layer dried. The solvent was evaporated and the residue purified by re-crystallisation from hot hexane to afford benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (11), (1.7 g, 97%), as white fibres, m.p. 80-82°C, $[\alpha]_D^{20}$ +75.0° (c, 1.7 in $CHCl_3$). υ_{max} ($CHCl_3$) 2120 cm^{-1}. ^1H NMR δ 1.37 (3H, s, CH_3); 1.57 (3H, s, CH_3); 1.93 (1H, dd, OH); 3.57-3.84 (4H, m, 4-H, 5-H, 6-H); 4.16 (1H, d, 2-H); 4.27 (1H, dd, 3-H); 4.62 (2H, ABq, $PhCH_2$); 5.17 (1H, s, 1-H); 7.32-7.41 (5H, m, ArH). m/z (DCI, NH_3): 353 ($M + NH_4^+$), 320, 308, 91 (100%) (Found : C, 57.61; H, 6.23; N, 12.44. $C_{16}H_{21}N_3O_5$ requires C, 57.32; H, 6.31; N, 12.53%).

Benzyl 4-Amino-4-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (12). Benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (11) (1 g, 3 mmol) was dissolved in methanol (10 ml) and added to a suspension of pre-reduced palladium black (0.2 g) in methanol (10 ml) under hydrogen at room temperature. After 1 h the catalyst was removed by filtration and the solvent evaporated to give benzyl 4-amino-4-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (12), (0.92 g, 100%), as a

clear syrup. ^{1}H NMR δ 1.34 (3H, s, CH_3); 1.51 (3H, s, CH_3); 2.33 (1H, br s, OH); 2.89 (1H, dd, 4-H, J_{45} 10.0Hz); 3.55 (1H, m, 5-H); 3.79 (2H, m, 6-H); 3.94 (1H, dd, 3-H, J_{34} 8.3 Hz); 4.12 (1H, d, 2-H, J_{23} 5.3 Hz); 4.61 (2H, ABq, $PhCH_2$); 5.14 (1H, s, 1-H); 7.2-7.3 (5H, m, ArH). m/z: (DCI, NH_3) 310 (M + H^+, 100%), 292, 202, 91.

Benzyl 4-Benzyloxycarbonylamino-4-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (13). A solution of benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (11) (1.1 g, 2.48 mmol) in methanol (60 ml) containing palladium black (0.24 g) was hydrogenated at room temperature for 2 h. The solution was filtered through celite and the solvent removed to afford a syrup. The crude amine was dissolved in ether (20 ml), saturated aqueous sodium bicarbonate solution (8 ml) and benzyl chloroformate (1 ml, 7.0 mmol) added at 0°C and the two phase reaction mixture was stirred for 1.5 h. The mixture was extracted into chloroform, dried and the organic layer concentrated to a solid which was recrystallised (chloroform : hexane) to give benzyl 4-benzyloxycarbonylamino-4-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (13), (1.3 g, 80%), m.p 157-158°C, $[\alpha]_D^{20}$ +45° (c, 0.8 in $CHCl_3$). ν_{max} (nujol) 3480, 3360, 1718 cm^{-1}. ^{1}H NMR δ 1.34 (3H, s, CH_3); 1.54 (3H, s, CH_3); 3.15 (1H, br, OH); 3.58 (1H, br d, 6-H); 3.7 (2H, m, NH, 4-H); 3.82 (1H, dd, 6-H); 4.15 (2H, m, 3-H, 2-H); 4.61 (2H, ABq, $PhCH_2$); 4.89 (1H, br d, 5-H); 5.04-5.2 (3H, m, $PhCH_2$, 1-H); 7.37 (10H, m, ArH). m/z (CI, NH_3): 353, 336, 108. (Found C, 65.2; H, 6.55; N, 3.1. $C_{24}H_{29}NO_7$ requires C, 65.0; H, 6.54; N, 3.16%).

1,4-Dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (14). Benzyl 4-amino-4-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (12) (0.92 g, 3 mmol) was dissolved in glacial acetic acid (10 ml) containing palladium black (0.2 g) and stirred under an atmosphere of hydrogen for 2 d. The catalyst was removed by filtration and the solvent evaporated. Purification of the residue by flash chromatography (gradient elution of methanol in chloroform) gave 1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (14), (0.58 g, 90%) as a brown oil, which was crystallised by extraction into ether and subsequent evaporation, m.p 86-88°C. $[\alpha]_D^{20}$ -53.3° (c, 0.43 in $CHCl_3$). ν_{max} 3600-3300, 2990, 1380, 1270, 1160 cm^{-1}. ^{1}H NMR (D_2O) δ 1.20 (3H, s, CH_3); 1.33 (3H, s, CH_3); 2.69 (1H, s, 1-H, $J_{1,2}$ 3.6 Hz); 2.82 (1H, dd, 4-H, $J_{3,4}$ 3.5 Hz, $J_{4,5}$ 9.2 Hz); 3.01 (1H, d, 1-H, $J_{1,1}$ 13.2 Hz); 3.45 (1H, dd, 6-H, $J_{5,6}$ 6.3 Hz); 3.61 (1H, dd, 6-H, $J_{6,6}$, 12.0 Hz, $J_{5,6}$ 3.3 Hz); 3.78 (1H, ddd, 5-H); 4.73-4.69 (2H, m, 2-H, 3-H). ^{13}C NMR δ 23.71 (q), 25.71 (q, CH_3C); 52.71 (t, 1-C); 64.83 (d, 4-C); 65.47 (t, 6-C); 71.30 (d, 5-C); 81.68 (d), 81.73 (d, 2-C, 3-C); 130.83 (s, CH_3C). m/z (ACE, NH_3): 204 (M + H^+), 142 (100%). (Found : C, 53.6; H, 8.2; N, 6.5. $C_9H_{17}NO_4$ requires C, 53.2; H, 8.4; N, 6.9%).

N-Acetyl-5,6-di-O-acetyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (15). 1,4-Dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (14) (50 mg, 0.25 mmol) was dissolved in pyridine (5 ml) and acetic anhydride (0.14 ml, 1.5 mmol) was added at 0°C. The reaction was allowed to warm to room temperature and stored for 8 h. The solvent was evaporated and the residue purified by flash chromatography to afford N-acetyl-5,6-di-O-acetyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (15), (43 mg, 53%), as a colourless oil which crystallised, m.p. 80-82°C, $[\alpha]_D^{20}$ -22.4° (c, 0.5 in $CHCl_3$). ν_{max} ($CHCl_3$) 1740, 1655 cm^{-1}. ^{1}H NMR δ 1.34 (3H, s, CH_3); 1.54 (3H, s, CH_3); 2.08, 2.05 (9H, 2s, CH_3CO); 3.38 (1H, m, 4-H); 3.9-4.8 (6H, m, 1-H, 2-H, 3-H, 6-H); 5.46 (1H, m, 5-H). m/z (DCI, NH_3) :347 (M + NH_4^+), 330, 270 (100%). (Found : C, 54.94; H, 7.17; N, 4.17. $C_{15}H_{23}NO_7$ requires C, 54.71; H, 6.99; N, 4.26%).

1,4-Dideoxy-1,4-imino-D-mannitol (2). 1,4-Dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (14) (50 mg, 0.25 mmol) was dissolved in trifluoroacetic acid : D_2O (9:1, 0.5 ml) and the reaction was monitored by observing the disappearance of the two isopropylidene proton resonances and appearance of the resonance for acetone in the 60 MHz NMR spectrum. After 48 h, the former had completely disappeared and the solvent was evaporated. Purification of the residue by ion exchange chromatography (CG 120, H^+ form, eluted with aqueous ammonia) gave 1,4-dideoxy-1,4-imino-D-mannitol (2), (30 mg, 73%), as a hygroscopic white solid, m.p. 137°C, $[\alpha]_D^{20}$ -10.4° (c, 0.12 in H_2O). ν_{max} (KBr) 3600-3300 cm^{-1}. ^1H NMR (D_2O) δ 2.58 (1H, dd, 1-H); 2.92 (1H, dd, 4-H, $J_{4,5}$ 10.0 Hz); 2.97 (1H, dd, 1'-H, $J_{1,1'}$ 11.3 Hz); 3.37 (1H, dd, 6-H, $J_{5,6}$ 6.3 Hz); 3.56 (1H, dd, 6'-H, $J_{6,6'}$ 11.3 Hz, $J_{5,6'}$ 3.8 Hz); 3.66 (1H, ddd, 5-H); 4.02 (1H, t, 3-H, $J_{3,4}$ 5.0 Hz); 4.13 (1H, dt, 2-H, $J_{2,3}$ 5.0 Hz, $J_{1,2}$ 8.1 Hz). ^{13}C NMR (D_2O) δ 48.52 (t, 1-C); 60.73 (d, 4-C); 63.59 (t, 6-C); 70.27 (d), 71.42 (d), 72.05 (d, 2-C, 3-C, 5-C). m/z (DCI, NH_3): 164 ($M + H^+$, 100%), 102. (Found C, 44.26; H, 8.13; N, 8.58. $C_6H_{13}NO_4$ requires C, 44.17; H, 7.98; N, 8.59%). The hydrochloride of (2) was more readily handled and is more easily crystallised, m.p. 148-149°C,. $[\alpha]_D^{20}$ -16.3° (c, 1.0 in H_2O). ^{13}C NMR (D_2O) δ 48.35 (t, 1-C); 63.26 (d, 4-C); 63.93 (t, 6-C); 66.23 (d), 70.76 (d), 70.95 (d, 2-C, 3-C, 5-C). (Found C, 36.09; H, 7.14; N, 6.99. $C_6H_{14}ClNO_4$ requires C, 36.10; H, 7.07; N, 7.02%).

N-tert-Butyloxycarbonyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (16). 1,4-Dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (14) (0.2 g, 0.99 mmol) was dissolved in dry pyridine (5 ml) and cooled to 0°C. Di-tert-butyl-dicarbonate (0.28 g, 1.3 mmol) was added and the solution stirred for 3 h. The reaction mixture was diluted with dichloromethane and washed successively with dilute hydrochloric acid, water and saturated aqueous sodium bicarbonate solution. The dichloromethane was dried and concentrated to a syrup which was purified by flash chromatography (ethyl acetate : hexane, 1:1) to yield N-tert-butyloxycarbonyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (16), (0.14 g, 47%), a syrup, $[\alpha]_D^{20}$ -44.5° (c, 0.16 in $CHCl_3$). ν_{max} 3450 (br), 1670 cm^{-1}. ^1H NMR δ 4.95 (1H, t, 3-H); 4.85 (1H, m, 2-H); 4.2-3.5 (7H, m); 3.2 (1H, dd, 1-H); 1.5, 1.3 (6H, 2s, CH_3CO); 1.4 (9H, s, tBu). m/z (DCI, NH_3): 304 ($M + H^+$), 248, 204 (100%). (Found C, 54.9; H, 8.4; N, 4.6. $C_{14}H_{25}NO_6$ requires C, 55.4; H, 8.3; N, 4.6%).

N-tert-Butyloxycarbonyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-lyxitol (17). N-tert-Butyloxycarbonyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-mannitol (16) (73 mg, 0.24 mmol) was dissolved in 50% aqueous ethanol (7 ml) and stirred at room temperature with sodium periodate (63 mg, 1.2 equivs). After 15 min, sodium borohydride (45 mg, 5 equivs) was added and the stirring continued for a further 30 min. The solution was filtered and evaporated; the residue was partitioned between chloroform and water. The chloroform layer was dried and concentrated and the residue purified by flash chromatography (ethyl acetate : hexane, 3:2) to yield N-tert-butyloxycarbonyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-lyxitol (17), (51 mg, 78%), a syrup. $[\alpha]_D^{20}$ -42.2° (c, 0.23 in $CHCl_3$). ν_{max} 3400 (br), 1680 cm^{-1}. ^1H NMR δ 1.4 (9H, s, tBu); 1.3 (3H, s, CH_3); 1.5 (3H, s, CH_3); 3.5-4.9 (8H, br m). m/z (DCI, NH_3): 291 ($M + NH_4^+$), 274, 218 (100%).

1,4-Dideoxy-1,4-imino-D-lyxitol Hydrochloride (3). N-tert-Butyloxycarbonyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-lyxitol (17) (29 mg, 0.11 mmol) was dissolved in trifluoroacetic acid / D_2O (1:1, 1 ml) and stored at room temperature. The progress of the hydrolysis was monitored by 60 MHz NMR. After 12 h, the solvent was removed and purification of the residue by ion exchange chromatography (Aldrich 50X 8-100, H^+ form, eluted with aqueous ammonia) and freeze drying afforded the

free base of (3), (10 mg, 68%), as a syrup. This syrup was dissolved in distilled water (0.5 ml) and acidified to pH 4 with dilute hydrochloric acid solution. When this solution was freeze dried, 1,4-dideoxy-1,4-imino-D-lyxitol hydrochloride (3), was obtained as a white solid, m.p. 159-161°C, $[\alpha]_D^{20}$ +19.8° (c, 0.45 in H_2O). ^1H NMR (D2O) δ 3.0 (1H, dd, 1-H); 3.4 (1H, dd, 1'-H); 3.55 (1H, m, 4-H); 3.7 (1H, dd, 5-H); 3.8 (1H, dd, 5'-H); 4.2 (1H, t, 3-H); 4.3 (1H, dt, 2-H). m/z: (DCI, NH_3) 134 ($M + H^+$, 100%).

Benzyl E-4-Azido-4,6,7-trideoxy-6-ene-2,3-O-isopropylidene-α-D-manno-octadialdopyranoside (18). Pyridinium chlorochromate (0.41 g, 1.9 mmol) and powdered molecular sieve (3A, 1 g) were added to a solution of benzyl 4-azido-4-deoxy-2,3-O-isopropylidene-α-D-mannopyranoside (11) (0.32 g, 0.96 mmol) in dry dichloromethane (20 ml) and the mixture was stirred at room temperature. After 45 min, formylmethylene triphenylphosphorane (2.0 g, 6.6 mmol) was added to the reaction mixture which was then stirred for a further 45 min. At this stage t.l.c (ether : hexane, 2:1) showed one major product (Rf 0.7) and several minor products (Rf 0.5-0.6). The solution was diluted with ether (20 ml) and filtered through a silica plug and the resulting solution concentrated to a syrup which was purified by flash chromatography (hexane : ether, 2:1) to yield benzyl E-4-azido-4,6,7-trideoxy-6-ene-2,3-O-isopropylidene-α-D-manno-octadialdopyranoside (18), (236 mg, 68%), which was recrystallised from methanol : water as white needles, m.p. 105-106°C. υ_{max} ($CHCl_3$) 3000, 2940, 2110, 1700, 1460, 1390, 1380, 1230, 1130, 1090, 1000 cm^{-1}. ^1H NMR δ 1.47 (6H, d, Me_2C); 3.38 (1H, dd, 4-H); 4.19-4.36 (3H, m, 5-H, 6-H); 4.60 (2H, ABq, $PhCH_2$); 5.22 (1H, s, 1-H); 6.47 (1H, ddd, 7-H); 6.87 (1H, dd, 6-H); 7.3-7.5 (5H, m, ArH); 9.61 (1H, d, -CHO). m/z (DCI, NH_3): 377 ($M + NH_4^+$), 360, 338, 248, 91 (100%). (Found : C, 60.24; H, 6.03; N, 11.53. $C_{18}H_{21}N_3O_5$ requires C, 60.16; H, 5.89; N, 11.69%). $[\alpha]_D^{20}$ +25.1° (c, 0.5 in $CHCl_3$). Also from the same column was isolated the dieneal (20), (35 mg, 12%), m.p. 83-84°C. ^1H NMR δ 1.40 (6H, d, Me_2C); 4.20 (1H, dd, 2-H); 4.71-4.88 (3H, m, 3-H and $PhCH_2$); 5.04 (1H, s, 1-H); 5.52 (1H, s, 4-H); 6.50 (1H, dd, 7-H); 6.78 (1H, dd, 6-H); 7.3-7.5 (5H, m, ArH); 9.63 (1H, d, -CHO). m/z (DCI, NH_3): 317 ($M + H^+$, 3%), 259 (13%), 167 (24%), 150 (10%), 91 (100%).

Benzyl 4-Benzyloxycarbonylamino-4,6,7-trideoxy-6-ene-2,3-O-isopropylidene-α-D-manno-octadialdopyranoside (19). A mixture of benzyl 4-benzyloxycarbonylamino-4-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (13) (0.98 g, 2.21 mmol), pyridinium chlorochromate (0.9 g, 4.17 mmol) and powdered molecular sieve (2.9 g) in dichloromethane (100 ml) was stirred at room temperature for 1.5 h. The mixture was diluted with ether and filtered through a silica plug (eluted with ether : hexane, 2:1) to give the corresponding aldehyde, (0.73 g, 75%), m.p. 49-52°C. υ_{max} ($CHCl_3$) 3530, 1750 cm^{-1}. ^1H NMR δ 1.25 (3H, s, CH_3); 1.45 (3H, s, CH_3); 4.08 (1H, d, 4-H); 4.18 (1H, d, 2-H); 4.35 (1H, br t, 3-H); 4.5 (1H, m, 5-H); 4.7 (2H, ABq, $PhCH_2$); 5.09 (3H, m, $PhCH_2$, 1-H); 6.0 (1H, br d, NH); 7.37 (10H, m, ArH); 9.68 (1H, s, 6-H). m/z (DCI, NH_3): 442 ($M + H^+$, 100%). The aldehyde was dissolved in dichloromethane (50 ml) and stirred at room temperature with formylmethylene-triphenylphosphorane (3.2 g, 9.95 mmol) for 16 h. The reaction mixture was filtered through a silica plug and the solvent evaporated to give a colourless foam which was purified by flash chromatography (ether : hexane, 1:1) to give benzyl 4-benzyloxycarbonylamino-4,6,7-trideoxy-6-ene-2,3-O-isopropylidene-α-D-manno-octadialdopyranoside (19), (0.61 g, 59%), m.p. 62-64°C, $[\alpha]_D^{20}$ +30.9° (c, 1.0 in $CHCl_3$). υ_{max} (KBr) 3380, 1725, 1690 cm^{-1}. ^1H NMR δ 1.21 (3H, s, CH_3); 1.34 (3H, s, CH_3); 3.75 (1H, m, 4-H); 4.25 (2H, m, 2-H, 3-H); 4.45 (1H, br t, 5-H); 4.6 (2H, ABq,

$PhCH_2$); 5.15 (4H, m, $PhCH_2$, 1-H, NH); 6.35 (1H, ddd, 7-H); 6.79 (1H, dd, 6-H); 7.32 (10H, m, ArH); 9.5 (1H, d, CHO). m/z (DCI, NH_3): 485 ($M + NH_4^+$), 468, 360 (100%).

1,2-O-Isopropylidene-Swainsonine (21). (i) From the azide (18). A solution of benzyl E-4-azido-4,6,7-trideoxy-6-ene-2,3-O-isopropylidene-α-D-manno-octadialdopyranoside (18) (210 mg, 0.58 mmol) in methanol (3 ml) was added to methanol (5 ml) containing pre-reduced 10% palladium on carbon (50 mg) and stirred under an atmosphere of hydrogen for 6 h. The catalyst was removed by filtration and the solvent evaporated to produce crude (22) as a colourless oil [see below for isolation]. The secondary amine (22) was added as a solution in acetic acid (3 x 1 ml) to a suspension of palladium black (50 mg) in acetic acid (9 ml) which had been pre-reduced under hydrogen, and the resulting mixture was stirred under an atmosphere of hydrogen at room temperature. After 3 d, the catalyst was removed by filtration and the solvent evaporated. Purification of the residue by flash chromatography (0-15% ethanol in chloroform) gave 1,2-O-isopropylidene-swainsonine (21), (107 mg, 87% from the enal (18), as white needles, m.p 106-108°C (lit.[2] m.p. 105-107°C). $[\alpha]_D^{20}$ -65.8° (c, 0.5 in MeOH) [lit.[2] $[\alpha]_D^{20}$ -75.1° (c, 1.54 in MeOH]. ^{1}H NMR δ 1.3 (3H, s, CH_3); 1.5 (3H, s, CH_3); 1.67 (4H, m, 6-H, 7-H); 1.86-2.10 (3H, m, OH, 8a-H, 5-Hax); 2.15 (1H, dd, $J_{2,3}$ 4.2 Hz, 3-H); 3.0 (1H, dt, 5-Heq, $J_{5e,5a}$ 10.6 Hz and $J_{5e,6}$ 3.4 Hz); 3.18 (1H, d, 3-H, $J_{3,3'}$ 10.6 Hz); 3.86 (1H, ddd, 8-H, J 4.6, 8.8, 9.0 Hz); 4.62 (1H, dd, 2-H, $J_{2,3}$ 4.2 Hz, $J_{1,2}$ 6.3 Hz); 4.7 (1H, dd, 1-H, $J_{1,8a}$ 4.5 Hz). ^{13}C NMR δ 23.95 (t), 24.77 (q), 25.86 (q), 32.98 (t), 51.57 (t), 59.82 (t), 67.3 (d), 73.65 (d), 78.19 (d), 79.12 (d) and 111.35 (s). m/z (EI): 213 (M^+), 113 (100%).).

(ii) from carbamate (19). Hydrogenation of the carbamate (19) under the same conditions as in (i) gave 1,2-O-isopropylidene-swainsonine (21) in 60% yield.

(1R,3S,4S,5S,6R)-7-Aza-3-benzyloxy-4,5-isopropylidenedioxy-2-oxa-bicyclo[4,4,0]-decane (22). A solution of benzyl 4-benzyloxycarbonylamino-4-deoxy-2,3-O-isopropylidene-α-D-manno-octadialdopyranoside (19), (0.25 g, 0.54 mmol), in methanol (15 ml) with palladium black (0.25 g) was hydrogenated for 48 h. The solution was filtered through celite and the solvent removed. The residue, which darkened on standing, could be purified by flash chromatography (ether : hexane, 1:1) with some loss of material to give (1R,3S, 4S,5S,6R)-7-aza-3-benzyloxy-4,5-isopropylidenedioxy-2-oxa-bicyclo[4,4,0]decane (22), (0.104 g, 61%), as an oil, ν_{max} (film) 3330 cm^{-1}. ^{1}H NMR δ 1.34 (3H, s, CH_3); 1.44 (2H, m, 9-H); 1.52 (3H, s, CH_3); 1.71 (1H, br d, 10-H); 1.99 (2H, br, NH, 10-H); 2.46 (1H, dd, 8-H); 2.59 (1H, dt, 8-H); 2.99 (1H, br d, 6-H); 3.43 (1H, dt, 1-H); 4.01 (1H, dd, 5-H); 4.14 (1H, d, 4-H); 4.65 (2H, ABq, $PhCH_2$); 5.12 (1H, s, 3-H); 7.31 (5H, m, ArH). m/z: (DCI, NH_3) 320 ($M + H^+$, 100%). A minor product of this reaction was the N-methylated product (23), ^{1}H NMR δ 1.34 (3H, s, CH_3); 1.38 (1H, m, 9-H); 1.52 (3H, s, CH_3); 1.72 (3H, m, 9-H, 10-H); 1.89 (1H, m, 8-H); 2.09 (1H, dt, 8-H); 2.4 (3H, s, NCH_3); 2.8 (1H, br d, 6-H); 3.54 (1H, dt, 1-H); 4.18 (2H, m, 4-H, 5-H); 4.65 (2H, ABq, $PhCH_2$); 5.08 (1H, s, 3-H); 7.32 (5H, m, ArH). m/z (DCI, NH_3): 334 ($M + H^+$, 100%).

Swainsonine [(1S,2R,8R,8aR)-1,2,8-Trihydroxy-octahydroindolizine] (1). 1,2-O-Isopropylidene-swainsonine (21) (42 mg, 0.197 mmol) was dissolved in trifluoroacetic acid : D_2O (4:1, 1 ml) and stored at room temperature for 50 h. The solvent was evaporated and the residue purified by ion exchange chromatography (CG 120 H^+ form, elute with aqueous ammonia) to give a yellowish solid, which was further purified by flash chromatography (ethanol : chloroform, 1:2) to give swainsonine (1), (25 mg, 74%), as white crystals, m.p. 141-143°C (lit.[2] 144-145°C), $[\alpha]_D^{20}$ -78.7° (c, 0.63 in MeOH) [lit.[2] $[\alpha]_D^{20}$ -87.2° (c 2.1, MeOH)]. ν_{max} (KBr) 3500 cm^{-1}.

^{1}H NMR δ 0.96-1.89 (6H, m, 8a-H, 5-H, 6-H, 7-H); 2.35 (1H, dd, 3H, $J_{2,3}$ 3.1 Hz, $J_{3,3'}$ 11.0 Hz); 2.74 (2H, m, 3'-H, 5'-H); 3.60 (1H, ddd, 8-H, $J_{7,8}$ 4.7 Hz, $J_{7',8}$ 10.1 Hz, $J_{8,8a}$ 9.5 Hz); 4.05 (1H, dd, 1-H, $J_{1,8a}$ 3.7 Hz, $J_{1,2}$ 6.1 Hz); 4.14 (1H, m, 2-H). m/z (EI): 173 (M^+), 113 (100%). This synthetic material was identical to an authentic sample of swainsonine.[20]

REFERENCES

1. S. M. Colegate, P. R. Dorling and C. R. Huxtable, Aust. J. Chem., 1979, 32, 2257.
2. M. J. Schneider, F. S. Ungemach, H. P. Broquist and T. M. Harris, Tetrahedron, 1983, 39, 29.
3. M. Hino, O. Nakayama, T. Tsuzumi, K. Adachi, T. Shibata, H. Terano, M. Kohsaka, H. Aoki and H. Imanaka, J. Antibiot., 1985, 38, 926.
4. H. P. Broquist, P. S. Mason, W. M. Hagler and T. M. Harris, Appl. Environ. Microbiol., 1984, 48, 386.
5. L. E. Fellows, Pestic. Sci., 1986, 17, 602 and references cited therein.
6. T. Kino, N. Inamura, K. Nakahara, S. Kiyoto, T. Goto, H. Terano, M. Kohsaka, H. Aoki and H. Imanaka, J. Antibiot., 1985, 38, 936.
7. G. W. J. Fleet, P. W. Smith, S. V. Evans and L. E. Fellows, J. Chem. Soc., Chem. Commun., 1984, 1240.
8. G. Palamarczyk, M. Mitchell, P. W. Smith, G. W. J. Fleet and A. D. Elbein, Arch. Biochem. Biophys., 1985, 243, 35.
9. P. F. Daniel, D. S. Newburg, N. E. O'Neil, P. W. Smith and G. W. J. Fleet, Glycoconj. J., in preparation.
10. T. Szumilo, G. P. Kaushal, H. Hidetaka and A. D. Elbein, Plant Physiol., 1986, 81, 383.
11. G. W. J. Fleet, S. J. Nicholas, P. W. Smith, S. V. Evans, L. E. Fellows and R. J. Nash, Tetrahedron Lett., 1985, 26, 3127.
12. G. W. J. Fleet and P. W. Smith, Tetrahedron, 1986, 42, 5685 and references cited therein.
13. M. H. Ali, L. Hough and A. C. Richardson, J. Chem. Soc., Chem. Commun., 1984, 447; M. H. Ali, L. Hough and A. C. Richardson, Carbohydr. Res.,1985, 136, 225; T. Suami, K. Tadano and Y. Iimura, Chem. Lett., 1984, 513; T. Suami, K. Tadano and Y. Iimura, Carbohydr. Res., 1985, 136, 67; N. Yasuda, H. Tsutsumi and T. Takaya, Chem. Lett., 1984, 1201; H. Setoi, H. Takano and M. Hashimoto, J. Org. Chem., 1985, 50, 3948; C. E. Adams, F. J. Walker and K. B. Sharpless, J. Org. Chem., 1985, 50, 421.
14. G. W. J. Fleet, M. J. Gough and P. W. Smith, Tetrahedron Lett., 1984, 25, 1853.
15. F. M. Winnik, J. P. Carver and J. J. Krepinsky. J. Org. Chem., 1982, 47, 2701.
16. P. A. J. Gorin and A. S. Perlin, Can. J. Chem., 1961, 39, 2474; J. Alais and A. Veyrieres, J. Chem. Soc., Perkin Trans. 1, 1981, 377.
1722. J. Herscovici and K. Antonakis, J. Chem. Soc. Chem. Commun., 1980, 561.
18. M. E. Evans, Carbohydr. Res., 1977, 54, 105; J. S. Brimacombe, F. Hunedy and A. K. Al-Radhi, Carbohydr. Res., 1969, 11, 331.
19. G. N. Austin, P. D. Baird, G. W. J. Fleet, J. M. Peach, P. W. Smith, and D. J. Watkin, Tetrahedron, accompanying paper.
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